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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/063,586   | 05/03/2002  | Dan L. Eaton         | 10466/353           | 2703             |
| 30313  | 7590        | 06/14/2005           | EXAMINER            |                  |
| KNOBBE, MARTENS, OLSON & BEAR, LLP<br>2040 MAIN STREET<br>IRVINE, CA 92614 |             |                      | KAUFMAN, CLAIRE M   |                  |
|  |             |                      | ART UNIT            | PAPER NUMBER     |
|  |             |                      | 1646                |                  |

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                                      |                                     |  |
|------------------------------|--------------------------------------|-------------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/063,586 | <b>Applicant(s)</b><br>EATON ET AL. |  |
|                              | <b>Examiner</b><br>Claire M. Kaufman | <b>Art Unit</b><br>1646             |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 4-8 and 11-17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 4-8 and 11-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/4/05</u> . | 6) <input type="checkbox"/> Other: _____  |

*RS*

### DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/05 has been entered.

### *Response to Arguments*

The rejections of claims 1-3 are moot in view of the cancellation of the claim.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 101/ 112, First Paragraph*

Claims 4-8 and 11-13 remain and new claims 14-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action, including those which address the new claims:

New claims 14-17 are drawn to a polypeptide at least 95% identical to SEQ ID NO:78 (with or without its signal sequence), which polypeptide or a fragment thereof can be used to generate an antibody that specifically detects SEQ ID NO:78 in lung or stomach tissue samples. Because as discussed in previous Office actions and below, the polypeptide of SEQ ID NO:78 does not have utility or enablement, an antibody which binds it likewise does not. As stated in the previous Office action mailed 3/8/05 (p. 2, end of last full paragraph), "If the polypeptide is not enabled then, an antibody which binds it is also not enabled." Detecting a polypeptide which does not meet the requirements for utility and enablement, does not provide a utility or enabling use for the compound used for detection. It is noted that the asserted utility for the nucleic acid of SEQ ID NO:77 or the coding region thereof has been accepted upon further reconsideration. However, nucleic acids which are not identical to SEQ ID NO:77 (or the coding region thereof) do not have utility for reasons set forth. Nevertheless, it is maintained that the encoded polypeptide of SEQ ID NO:78 (PRO1357) does not have utility or enablement for the reasons of

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record, particularly the lack of predictability of the correlation between mRNA and protein levels.

Claims 4-8 and 11-13 remain and new claims 14-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above and in the previous Office action, one skilled in the art clearly would not know how to use the claimed invention.

Applicants arguments under 35 USC 101 also support the request to withdraw the related rejection under 35 USC 112, first paragraph, enablement (p. 28 or response). As a result, both utility and enablement arguments will be discussed here.

Applicants argue (p. 7) that the phrase “immediate benefit to the public” does not necessarily have to mean the invention is “currently available” to the public in order to satisfy utility requirements. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining ‘substantial’ utility.” (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when “further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101. For reasons discussed at length in the previous Office action, even if the encoding polynucleotide has utility, one cannot on that basis alone support a utility for the encoded protein because the prior art provides sufficient support to make a correlation between mRNA and encoded protein level unpredictable (*e.g.*, Konopka et al, PNAS 1986, and Haynes et al., Electrophor. 1998), especially in cancerous tissue (*e.g.*, see Hu et al., J. Proteome Res. 2003).

Applicants argue on pages 7 and 9-10 that *In re Brana* states that “Usefulness in patent law... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to administer to humans.” The argument has been fully considered, but is not persuasive. While *Brana* did deal with a rejection under 35 USC 112, first paragraph, the rejection was direct toward utility—

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specific, substantial and credible use—instead of enablement. While it is true that administration of a pharmaceutical to a human is not always necessary for either utility or enablement, one must know how to use the invention without undue experimentation. In the instant situation, Applicants claim a polypeptide which is at least 95% identical to SEQ ID NO:78, which it is maintained the disclosure does not enable the use of.

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is a polypeptide encoded by a nucleic acid with no known specific association other than that asserted by Applicants of underexpression in stomach and lung tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in stomach and lung tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical property. Proteins not identical to SEQ ID NO:78 have not been shown to exist in nature, let alone in stomach or lung tissue. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though none as a tumor marker were identical or highly similar to SEQ ID NO:77. Therefore, the connection of SEQ ID NO:77 to tumors was not known. The prior art is silent with respect to activity of PRO1357 or its relationship to a family of proteins with conserved structure and function. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. The breadth of the claims is broad, encompassing structural variation. There is very little guidance or direction about using the claimed polypeptide except that the encoded nucleic acid of SEQ ID NO:77 is underexpressed in stomach and lung tumors. As discussed in previous Office actions, the specific type of tumor is not disclosed, nor are levels of expression, relative

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amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

On page 8, Applicants cite *Fujikawa v. Wattanasin* and *Cross* cases, arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo*. The argument has been fully considered, but is not persuasive. As stated in the previous Office action mailed 3/4/05, "At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: whether differences in nucleic acid expression of PRO1357 were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention."

Applicants argue (pages 9-10) that there is a "significant probability" that the expression of the polypeptide will correlate with encoding nucleic acid expression. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential prior art of record that requires the Examiner maintain that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:77 positively correlates with the expression of the protein of SEQ ID NO:78. The prior art supports. As stated in the Office action mailed 12/13/04, "For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease." (p. 5) "Indeed, there is evidence in the art to refute generalizations about gene/protein correlations. For example, Haynes et al. (Electrophoresis 19 : 1862-1 871 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA

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levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Konopka et al. (PNAS, 83:4049-52, 1986) states that, "Protein expression is not related to amplification of the *abl* gene, but to variation in the level of bcr-abl mRNA production from a single Ph1 template" (see abstract). Konopka et al. also provide evidence showing lack of correlation between gene amplification and increased polypeptide levels. Haynes et al. provides evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the unknown amount that DNA copy number of PRO1357 decreased in tumors, and the evidence provided by Haynes et al., Hu et al. (discussed above) and Konopka et al., one skilled in the art would not have assumed that a small decrease in gene copy number would correlate with significantly increased mRNA or polypeptide levels. The level of decrease of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO1357 polypeptide levels decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Note that the invention must have a specific and substantial utility." (p. 7-8)

As was stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more

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specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form

Applicants argue (p. 11, #3) that “Polypeptides such as PRO1357 which are differentially expressed in certain cancers are useful as diagnostic tools.” The argument has been fully considered, but is not persuasive. Were PRO1357 differentially expressed and were this expression significant, repeatable and the information sufficiently complete to allow use of the polypeptide without undue experimentation, it would have utility as a diagnostic tool. It, however, has none of these necessities. There is no showing or reasonable expectation that PRO1357 is differentially expressed in certain cancers, even though its encoding nucleic acid of SEQ ID NO:77 appears to be underexpressed in stomach and lung tumors, though specifically which kind and at what levels is unknown.

Applicants argue (pp. 12 –15 and 27) that the data in Example 18 as discussed in the Declaration of Grimaldi demonstrates at least a two-fold difference in expression between normal and tumor tissues and the usefulness of the encoding nucleic acid as a diagnostic tool for determining the presence or absence of a tumor. The argument has been fully considered, but is not persuasive. The conclusory statement of Grimaldi of the necessary existence of an at least two-fold differentiation in nucleic acid expression does not support a utility for or enable the invention because it does not fill important gaps in the disclosure needed to use the invention without significant further experimentation, such as expression level range for normal and tumor tissues, specific types of stomach or lung tumors detectable, and probability of detection for any particular stomach or lung tumor type (*e.g.*, whether one would reasonably expect underexpression in 10/10 or 1/20 tumors tested), or if and how much the PRO1357 polypeptide is expressed in normal *versus* tumor stomach and lung tissue. Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues, this does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as “semi-quantitative” and the specification for Example 18 as “standard quantitative”. The declaration also says (§5) that “Data from a pooled sample are more likely to be accurate than data from a single individual.” This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical



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diagnostics are not usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of stomach or lung tissue that can be used, and other questions, the specification has not provided the invention in an enabling form. Therefore, even accepting Dr. Grimaldi's opinion (see first paragraph of p. 13 of response), the declaration is insufficient to overcome the rejections of the claims under 35 USC 101 or 112, first paragraph, for the reasons discussed above.

Applicants argue (pp. 14-15) that the Office cannot require experimental details to sufficiently establish utility of the claimed subject matter and the subject matter does not need to be "currently available". The argument has been fully considered, but is not persuasive. The Office is not requiring anything. The specification has failings which the Examiner pointed out. While current availability of a claimed invention is not always necessary, the invention must still meet the requirements of 35 USC 101 and 112, first paragraph. 35 USC 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...." For the reasons discussed here and in previous Office actions, it is maintained the specification does not contain an enabling disclosure or provide a specific and substantial credible utility or a well established utility, and the declarations previously submitted do not overcome the insufficiencies of the disclosure.

Applicants argue (p. 16-17 and 27) that the report of Haynes et al. and Gygi et al. (Mol. Cell. Biol., 1999) do not support the Examiner's position that mRNA levels do not correlate with protein levels, pointing out that Haynes did not look at *single* genes and corresponding protein level. The argument has been fully considered, but is not persuasive. A complete reading of Haynes and Gygi et al. continues to support the reliance on Haynes et al. Applicants' point to the correlation coefficient of 0.935 in Haynes et al., saying that this shows a correlation instead of the lack of one. However, a full reading of Haynes et al. clarifies the data (p. 1726, first full paragraph):

For the entire group (106 genes) for which a complete data set was generated, there was a

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general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data set (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was 0.356.

Contrary to Applicants' assertion that Figures 5 and 6 of Gygi support the correlation of mRNA and protein levels, Gygi et al. show in Figure 5 the same figure as Fig. 1 of Haynes and show in Fig. 6, what is described for the Pearson correlation coefficients in the cited paragraph above. Gygi et al. say beginning in the last sentence in col. 1 of p. 1727 that, "The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." As to correlation of an individual gene, Gygi et al. and Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described above by Haynes et al. Each point in the figures of Haynes et al. and Gygi et al. are individual genes (see Fig. 1 and Figs. 5-6, respectively). Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1357 nucleic acid was isolated)..

Applicants argue that Konopka et al. looked at gene amplification and protein level for bcr-able, finding a lack of correlation, though the mRNA and protein level did correlate. This argument is conceded, however, this exception looking at a single protein and gene does not support the opposition position of strong predictability of correlation between mRNA and protein level. Other references have been reviewed here and in previous Office actions which support the unpredictability by examining not just one, but a hundred or hundreds of mRNAs and corresponding proteins.

Applicants argue (pp. 19-20 and 27) that the declarations of Grimaldi and Polakis support the teachings in Molecular Biology of the Cell, Genes VI, and Zhingang et al. (2004), that it is generally accepted that mRNA and protein expression are positively correlated. The argument has been fully considered, but is not persuasive. As discussed above, there is sound supporting evidence showing the unpredictability of saying level of expression of a particular nucleic acid will correlate with expression of the encoded protein. The argument of correlation between nucleic acid and protein expression has been previously addressed. Zhighan find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application, we have no correlation. There is no suggestion of multiple tumors tested. There are [0530] just “cDNA libraries isolated from different human tumor and normal human tissue samples.” The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect underexpression in 10/10 or 1/20 tumors tested for the PRO1357 nucleic acid and/or protein. If Zhinghan et al. had obtained only a 5% correlation, it is doubtful he would have concluded that the nucleic acid would be a promising molecular marker.

Applicants argue the Meric et al. (Mol. Cancer Ther., 2002) says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this statement is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use as discussed above.

Applicants argue (p. 23) that the results of Hu et al. (J. Proteome Res., 2003, previously cited) are not surprising and provide little if any information about genes with less than 5-fold differential expression tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: “It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are

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biologically meaningful.” As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are significant.

Applicants argue (p. 24) that the role of a gene in a cancer is not necessary to enable its use as a diagnostic tool for tumor detection. The argument has been fully considered, but is not persuasive. It is correct that the role of a gene need not be known, but the specification and/or prior art needs to enable that particular gene to be used diagnostically. In this case, the prior art provides no information about the use of the gene and the specification does not provide an enabling disclosure for use of the PRO1357 nucleic acid or protein as a diagnostic tool for stomach or lung tumors based on differential expression for the reasons discussed above and in previous Office actions. As to the claims drawn to proteins not identical to SEQ ID NO:78, even if SEQ ID NO:78 was enabled for a diagnostic tool, proteins not identical would not be because they would not be expected to be present in tumors and what parts of the protein are antigenic and necessary for proper antibody binding (and production) for the protein to be useful as an antigen to make antibodies that would recognize the protein of SEQ ID NO:78.

Applicants argue (p. 26-27) that the claimed invention has a specific utility as a cancer diagnostic tool, particular stomach and lung. The argument has been fully considered, but is not persuasive. While it is agreed that the polynucleotide of SEQ ID NO:77 has this specific utility, it is not agreed that the polypeptide of SEQ ID NO:78 does. The reasons for this have been discussed at length above, but include relative or absolute levels of the difference(s) in PRO1357 protein level in tumor vs. normal stomach or lung tissue, the lack of information about particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), the lack of information about repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and the unpredictability of correlation mRNA and protein expression levels, it is maintained that the claimed invention is not supported by a substantial or specific utility nor is it enabled.

### ***Claim Rejections - 35 USC § 112.***

Claims 4, 5, 12, 13 remain and new claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action

Applicants argue (p. 29-31) that if there are sufficient identifying characteristics, *e.g.*, functional characteristic coupled to a structure, sufficient for written description. In the instant application the function is expression of the encoding nucleic acid in normal stomach and lung or higher expression there than in stomach or lung tumor. The argument has been fully considered, but is not persuasive. The point is that **not** all polypeptides 95% or 99% identical to SEQ ID NO:78 are included. Only those that naturally occur in stomach or lung are included. Applicants have disclosed no concept of which protein(s) which is not identical to SEQ ID NO:78 is present in stomach or lung. The specification does not convey to one of skill in the art, including recombinant DNA/protein technology art, that the inventors were in possession of these non-identical naturally occurring claimed proteins. The specification does not provide information so the skilled artisan could readily envision such proteins. For these reasons and those previously of record, the rejection is maintained.

### ***Claim Rejections - 35 USC § 102***

Claims 4-8 and 11-13 remain and new claims 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/16318 or WO 00/12708 for the reasons set forth in the previous Office action.

Applicants argue that the instant application receives an effective filing date of 08/24/00 because the data of Example 18 was disclosed therein. The argument has been fully considered, but is not persuasive. Because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, as discussed above, and the earlier application likewise do not meet those requirements, the instant application does not receive benefit of priority to earlier filed applications. Even though SEQ ID NO:77 and 78 and the expression information of Table 18 were previously disclosed, enablement thereof has not been established as discussed above.

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***Conclusion***

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 9:00AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

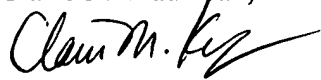
Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

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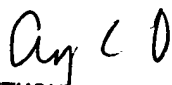
Art Unit: 1646

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